

## W11: Functional Pain Syndromes: Bidirectional Influences in Visceral Nociceptive Processing

Workshop Chair: Matthew Fraser, United States

27 August 2013 09:00 - 10:30

Start	End	Topic	Speakers
09:00	09:25	Visceral Nociceptive Processing in the Periphery	<ul style="list-style-type: none"> <li>• Lori Birder</li> </ul>
09:25	09:30	Questions	<ul style="list-style-type: none"> <li>• Lori Birder</li> </ul>
09:30	09:55	Visceral Nociceptive Processing in the Dorsal Root Ganglia and Spinal Cord	<ul style="list-style-type: none"> <li>• Matthew Fraser</li> </ul>
09:55	10:00	Questions	<ul style="list-style-type: none"> <li>• Matthew Fraser</li> </ul>
10:00	10:25	Visceral Nociceptive Processing in the Brain	<ul style="list-style-type: none"> <li>• Emeran Mayer</li> </ul>
10:25	10:30	Questions	<ul style="list-style-type: none"> <li>• Emeran Mayer</li> </ul>

### **Aims of course/workshop**

This workshop will describe nociceptive processing from pelvic viscera to the spinal cord, brain stem and the brain under normal conditions and how changes in bidirectional interactions may result in functional pain syndromes. Convergent evidence from patient populations with functional pain syndromes, including urologic chronic pelvic pain syndromes (UCPPS) and irritable bowel syndrome (IBS), suggests alterations in emotional arousal circuits and corticolimbic inhibition circuits, which facilitate and inhibit pain perception, respectively. In persistent pain conditions, it is believed that alterations in these interoceptive influences result in chronic visceral hyperalgesia.

## **Functional Pain Syndromes: Bidirectional Influences in Visceral Nociceptive Processing**

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Various hypotheses abound regarding the etiology of functional pain disorders, including urologic chronic pelvic pain and irritable bowel syndrome. These range from a bottom-up, periphery-driven central sensitization to a top-down, psychogenic-driven interoceptive process. We will provide the basis for a unifying theory which embraces bidirectional interactions as the likely explanation for functional pain disorders. In order to accomplish this goal, an overview of peripheral processing of visceral nociception, spinal level processing and central cognitive influences on final pain perception. By the end of the workshop, the audience will be well educated in nociception from the bottom up and mechanisms by which top-down influences may be realized.

The speakers are all experts in the field of visceral nociception. This workshop is the result of an ongoing interaction among the speakers and will cover their interests in nociceptive processing and functional pain syndromes. The Chair will briefly introduce the topic and speakers. Dr. Birder will then describe visceral sensation and nociception by neural and non-neural cell types at the level of the target tissue, in this case the urinary bladder. After a brief Q/A session, Dr. Fraser will follow with a talk that describes afferent processing from the target through the spinal cord to the brainstem and brain, and introduce the concepts and putative mechanisms of bidirectionality. After a brief Q/A session, Dr. Mayer will discuss the differences in brain processing, as measured by functional imaging and psychological testing, among unaffected individuals and sufferers of functional brain disorders. A final Q/A session will end the workshop.

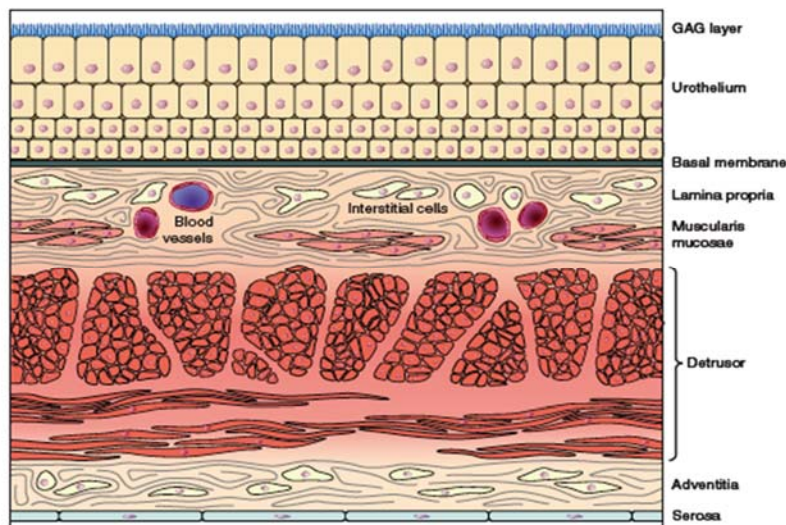
## Visceral Nociceptive Processing in the Periphery

Dr. Lori A. Birder, Ph.D.

Departments of Medicine and Pharmacology, University of Pittsburgh School of Medicine,  
Pittsburgh, PA, USA

The bladder mucosa, consisting of the urothelium, basement membrane, and underlying lamina propria (the sensory web), works in concert with other components in the bladder wall. The urothelium not only forms as a highly efficient barrier to potentially harmful urine components, but also exhibits properties similar to those of nociceptive and mechanoreceptive afferent neurons. Activation of the urothelial cells by chemical; thermal, or mechanical stimuli can evoke the release of various mediators or neurotransmitters that through the sensory web can influence nerve activity, detrusor cell contraction, and ultimately bladder function.

The lamina propria with its several types of interstitial cells and afferent nerves may act as a coordination center for bladder activity both during bladder filling and for initiation of the micturition reflex, thus having an important integrative role in, e.g., signal transduction to the central nervous system (nociception, mechanosensation). The mucosa undergoes important changes in many bladder diseases such as bladder pain syndrome, and is an important target for treatment. It is likely that a cascade of urothelial inhibitory and stimulatory transmitter/mediators are involved in the transduction mechanisms underlying the activation of afferent fibers during bladder filling. In this manner, the urothelium is likely to play an important role in the complex transfer of information to and from the nervous system. The urothelium is able to respond to a wide variety of mechanical stresses during bladder filling and emptying by activating a number of possible transducer proteins. This mucosal activation pathway (the sensory web) includes the urothelium, the afferent (and efferent) nerves, the ICs of the lamina propria, and possibly the muscularis mucosae. It is clear that communication between these different structures ensures normal function of the organ and may explain how the effect of various neurotransmitters/mediators when given intravesically can modify bladder function by changing neurotransmission, the spontaneous activity of the detrusor smooth muscle, and thereby bladder function.



Cartoon depicting various components within the urinary

Additional lines of evidence suggest that urothelial cells participate in the detection of both physical and chemical stimuli. Bladder nerves (afferent and efferent) are localized in close proximity to, and some within, the urothelium. In addition, urothelial cells express numerous receptors/ion channels similar to what is found in both nociceptors and mechanoreceptors elsewhere in the body, and these cells secrete a number of transmitters or mediators capable of modulating, activating, or inhibiting sensory neurons. In addition, various stimuli can also lead to secretion of chemical substances capable of modulating the activity of underlying smooth muscle. For example, urothelial-specific overexpression of nerve growth factor (NGF) results in increased bladder nerve 'sprouting' and increased voiding frequency.

*Some of the hypotheses and questions addressed by this workshop include:*

- 1) *What are the environmental cues that trigger urothelial responses within the bladder wall?*
- 2) *How are the urothelium and underlying cell types affected by pathology?*
- 3) *What is the nature of signaling between the urothelium and suburothelium?*
- 4) *Can pathophysiology at one site (e.g. urothelium) induce long-term changes at more distant sites along the sensory pathway?*

## Visceral Nociceptive Processing in the Dorsal Root Ganglia and Spinal Cord

Dr. Matthew O. Fraser, PhD

Division of Urology, Department of Surgery, Duke University and Durham VA Medical Centers,  
Durham, NC, USA

We will continue using the urinary bladder as an example, although much of what I will describe applies equally well to other pelvic viscera. As Dr. Birder described, the urinary bladder contains several non-neuronal cell types, such as epithelia, interstitial cells and even smooth muscle, which transduce environmental changes into biological signals, resulting in a transmural “sensory web” that interacts with nociceptive afferents. The afferents themselves can release mediators affecting their and sensory web sensitivity to stimuli. The final, integrated output leaves the viscera and traverses nociceptive axons to enter the spinal cord dorsal horn, and thus interaction with the central nervous system ensues.

So, let’s entertain the scenario that the bladder has been insulted by a urinary tract infection. The urothelium itself and urine infiltrates from broken barrier function will act on the sensory web and produce a level of signal that stimulates the afferents. Within the distance between the bladder and the spinal cord, several points of excitatory interaction occur with both other afferents from the bladder itself as well as afferents from neighboring viscera. We will refer to sensitization of afferents from the same organ as homosensitization, while sensitization of afferents from neighboring organs will be referred to as heterosensitization. But even before leaving the bladder, the efferent action of nociceptive afferents can locally not only sensitize the afferents that released the transmitter, but can sensitize other afferents in close proximity within the same organ, and these latter afferents may or may not be of the same phenotype (e.g. peptidergic vs. non-peptidergic nociceptors). So, within the bladder itself, homosensitization is likely.

Approximately 15-20% of C-fiber nociceptors have divergent axons that project to more than one pelvic visceral organ, and may project to one viscera and one other tissue types (e.g. skin, striated muscle). Here is the first opportunity for heterosensitization, as at the point of axon divergence, signals arising from the insulted organ backfire the divergent axon projecting to the other organ. This backfired nociceptor can also cause neurogenic inflammation by releasing its transmitters. Thus, now the non-insulted organ experiences inflammation as if it had been insulted. In a manner identical to the insulted organ, within organ homosensitization now ensues. The potential for reverberation within the pelvic region is high, as divergent axon projections have been reported between several pelvic organs.

At the level of the Dorsal Root Ganglion, cell-to-cell interactions can occur both by direct contact via projections (neurotransmission) and via local paracrine “field” transmission between afferent soma and glia. Stimulated soma can once again backfire to other or the same organ, providing another point and mechanism for both homo- and heterosensitization.

Within the spinal cord, field effects of released nociceptive transmitters and neuroinflammatory mediators by primary afferents as well as interneurons and glia can cause Dorsal Root Reflexes (DRR), which are afferent backfiring with its origins within the dorsal horn. DRR are also known to cross over to the contralateral side. Once again, homo- and heterosensitization can occur. Under normal circumstances, descending inhibition puts the brakes on DRR, as well as on the ascending pain information, such that painful peripheral stimuli do not become chronic “idiopathic” pain syndromes.

This speaks to the importance of the brain in sensing and responding to ascending nociceptive input. In addition to aversive and protective behaviors, the brain controls the descending inhibitory and excitatory inputs to the dorsal horn, and thus acts as the gatekeeper to its own inputs. Thus, if descending input is faulty, the peripheral and spinal positive feedback cascades of nociception described earlier may become more reality than possibility. Dr. Mayer will describe the brain's response to interoceptive stimuli, and how this may influence whether or not chronic pain syndromes evolve in an individual.

## Visceral Nociceptive Processing in the Brain

Dr. Emeran A. Mayer, MD

Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

One of the major functions of the mammalian brain is to detect events with salience for the organism and to respond to such events with the appropriate behavioral and neuroendocrine responses. In the healthy person, nociceptive events are generally salient, as they signal an event which may be harmful to the individual. However, conscious awareness of such events, in particular if they arise in the viscera is not always a prerequisite for an adaptive response. While acute inflammatory, infectious or obstructive events in the urinary or the digestive system are generally associated with significant symptoms, chronic low grade inflammation often is asymptomatic, presumably due to the engagement of powerful endogenous antinociceptive mechanisms by the brain. One of the hallmarks of “functional” visceral pain syndromes such as IBS and IC/PBS, is the fact that patients are hypervigilant towards normal and abnormal visceral signals, attribute greater salience to such signals, generate aberrant autonomic nervous system responses, and experience symptoms of pain and discomfort in the absence of detectable nociceptive events in the target organ.

With the application of imaging techniques to study alterations in brain structure and function, it has become possible to identify some of the brain circuits which underlie these abnormal responses. Demonstrated functional abnormalities in IBS and IC/PBS patients include abnormal engagement of emotional arousal/salience circuits, of cortico-limbic-pontine pain modulation circuits and of somatosensory and viscera sensory processing and modulation circuits. These functional abnormalities are accompanied by structural brain abnormalities (regional increases and decreases of grey matter, abnormal white matter tracts) in regions belonging to circuits that also show functional abnormalities. Some of the observed brain alterations are similar between IBS and IC/PBS patients, but are different between male and female patients. Big data approaches to multimodal brain imaging data may make it possible to identify brain signatures which represent biomarkers, correlate with patient subgroups, and predict outcome. Correlations of such brain signatures with behavioral, clinical and biological readouts, including multi-omics data is likely to provide insights into the pathophysiology of these disorders.

Selected references:

1. Ellingson, BM, Mayer EA, Ashe-McNally C, Naliboff BN, Labus JS, Tillisch K. Microstructural changes in the brain associated with chronic irritable bowel syndrome (IBS): A population-based diffusion tensor imaging (DTI) study, **Pain** 2013
2. **Mayer EA**, Tillisch K. Brain Gut Interactions. **Annu Rev Med** 62:381-96, 2011.
3. **Mayer EA**. Gut feelings: the emerging biology of gut-brain communication. **Nat Rev Neurosci** 12:453-66, 2011.

